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Use of Evidence-Based Therapies in and Short-term Outcomes of STEMI and NSTEMI in Patients with Chronic Kidney Disease: A Report from the National Cardiovascular Data ACTION Registry

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Abstract

Background—Chronic kidney disease (CKD) is a risk factor for myocardial infarction (MI) and death. Our goal was to characterize the association between CKD severity and short-term outcomes and the use of in-hospital evidence-based therapies among patients with STEMI and NSTEMI.

Methods and Results—The study sample was drawn from the ACTION Registry, a nation-wide sample of STEMI (n=19,029) and NSTEMI (n=30,462) patients. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation in relation to use of acute (first 24 hours) therapies and early (first 48 hours) cardiac catheterization as well as in-hospital major bleeding events and death. Overall, 30.5% and 42.9% of patients with STEMI and NSTEMI, respectively, had CKD. Regardless of MI type, patients with progressively more severe CKD had higher rates of death. For STEMI, the odds ratio for Stage 3a, 3b, 4, and 5 CKD compared to patients with no CKD was 2.49, 3.72, 4.82, and 7.97 (p-value for trend<0.0001). For NSTEMI, the analogous odds ratios were 1.81, 2.41, 3.50, and 4.09 (p-value for trend<0.0001). In addition, patients with progressively more severe CKD were less likely to receive acute evidence-based

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Conflict of Interest Disclosures

The authors report the following conflicts of interest: Kontos-Speakers Bureau: Sanofi-Aventis, Schering-Plough, Pfizer; Consultant: Sanofi-Aventis, Schering-Plough, Pfizer; Inovise Technologies, Mollecular Insight Pharmaceuticals; Research Support: Amersham/GE, Inovise Technologies, Biosite, Molecular Insight Pharmaceuticals; Saucedo –Eli Lilly, Bristol Myers Squibb/Sanofi, The Medicines Company, Research and Honoraria from Schering Plough, Honoraria Pfizer; Alexander-no conflicts, Wiviott- Sanofi - Aventis: Consulting; Eli Lilly -Research, Honoraria; Daiichi Sankyo -Research, Honoraria; Astra-Zeneca - Honoraria; Schering-Plough: Research, Pfizer - Honoraria, Roe- Receives research funding and serve as a consultant and member of the speakers bureaus for the companies that fund the ACTION registry via the American College of Cardiology - BMS/Sanofi-Aventis, and Schering-Plough. Cannon-Research grants/support from the following companies: Accumetrics, AstraZeneca, Bristol-Myers Squibb/Sanofi Partnership, Glaxo Smith Kline, Merck, Merck/Schering Plough Partnership; Clinical Advisor, equity in Automedics Medical Systems. The remainder of the authors report no conflicts

therapies including aspirin, beta-blockers or clopidogrel, undergo any reperfusion (STEMI) or revascularization (NSTEMI), and had higher rates of bleeding.

Conclusions—Reports over the past decade have highlighted the importance of CKD among patients with MI. Data from this contemporary cohort suggest patients with CKD still receive fewer evidence-based therapies and have substantially higher mortality rates.

Keywords

Chronic kidney disease; end-stage renal disease; dialysis; STEMI; NSTEMI; outcomes; resource utilization

Introduction

Kidney disease affects 26 million adults in the United States,[1] and nearly half a million individuals in the United States have end-stage renal disease.[2] Chronic kidney disease (CKD) is associated with an increased risk for cardiovascular disease,[3–5] stroke,[6] peripheral arterial disease,[6;7] and all-cause mortality.[8] Hypertension, dyslipidemia, and diabetes mellitus are common among patients with chronic kidney disease (CKD) but are often inadequately treated in this population.[9]

Results from previous studies indicate that patients with CKD, and particularly those undergoing dialysis, are known to have poor outcomes following the occurrence of acute coronary syndromes.[10–24] However, several of these studies have been limited to dialysis patients; and others are secondary analyses of clinical trial data with strict inclusion and exclusion criteria with respect to moderate and severe CKD. Because patients with CKD have been systematically excluded from clinical trials,[25;26] the prevalence and outcomes for patients with varying degrees of CKD (particularly stages 3–5), patients commonly seen in clinical practice, have not been well studied in the post-myocardial infarction (MI) setting. As such, previous findings are of limited utility in understanding the relationship between the severity of CKD and outcomes in unselected patient populations.

Therefore, the purpose of this analysis is to characterize the short-term outcomes related to CKD in a large hospital-based registry of post-MI patients. Despite a high-risk of adverse outcomes, we hypothesized that patients with CKD would be less likely to receive proven beneficial procedures and medications than their counterparts without CKD.

Methods

Study Sample

Patients for this study were drawn from the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) registry, a nationally-representative, quality improvement registry of ST segment elevation myocardial infarction (STEMI) and non- ST segment elevation myocardial infarction (NSTEMI) that began enrolling patients January 1, 2007. Data for the present analysis includes patients from the January 1, 2007 to December 31, 2007 study period at 280 ACTION Hospitals. Participating hospitals are required to submit data to the ACTION registry for all patients who presented within 24 hours of the onset of an ischemic syndrome, and if the primary diagnosis was myocardial infarction (either NSTEMI or STEMI). All participating centers are required to abide by local institutional review or ethical review standards. Baseline characteristics and key outcome data were extracted to a web-based case record form from existing medical records using a trained data collector at each hospital using standard definitions, and did not require direct contact with individual patients. A listing of specific data fields and definitions is

available at http://www.ncdr.com/WebNCDR/ACTION/Elements.aspx. Data quality and completeness is monitored by the NCDR Data Quality Program. The NCDR ACTION Registry is administered by the American College of Cardiology Foundation (ACCF) and sponsored by Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, Genentech, and Schering-Plough Corporation who provide material support for the operation of the data collection and infrastructure. The sponsors had no additional role in this project including the selection of topic, analysis of data, decision to publish, or approval of the manuscript prior to publication. Data analysis was performed by a statistician independent of the sponsors (AYC) from the Duke Clinical Research Institute. The authors had access to the data and take full responsibility for its integrity. CKD assessment, covariates definitions, and statistical methods can be found in the online supplement.

Results

Study Sample Characteristics

Overall, 19,029 STEMI and 30,462 NSTEMI patients were included in the present analysis; 30.5% and 42.9% of patients with STEMI and NSTEMI, respectively, had CKD of stage 3 or greater (Figure 1). Each stage of CKD (3b, 4, 5, dialysis) was more prevalent in patients with NSTEMI than those with STEMI, with the exception of Stage 3a (Figure 1). With progressively increasing CKD stage, patients were more likely to have hypertension, diabetes mellitus, and prior MI, CHF, and stroke. Additionally, patients with CKD were less likely to be current smokers and had lower BMI levels (Table 1).

Short-term outcomes by CKD Stage

Overall, the risk of mortality increased with CKD stage (Figure 2). Among patients who presented with STEMI, 2.3% of those without CKD died, compared to 8.8%, 17.9%, 27.3%, and 31.8% of those with Stage 3a, 3b, 4, and 5 CKD, respectively. In general, a similar trend was observed for NSTEMI, although the absolute event rates were substantially lower. For STEMI, the odds ratio for Stage 3a, 3b, 4, and 5 CKD relative to no CKD was 2.5, 3.7, 4.8, and 8.0 (p-value $_{(trend)}$ <0.0001). For NSTEMI, the odds ratios were 1.8, 2.4, 3.5, and 4.1 (p-value $_{(trend)}$<0.0001). However, there was a greater relative increase in death for patients with STEMI with advancing CKD stage than was seen in NSTEMI (p-value $_{(interaction)}$ <0.0001). Also, patients with CKD were at higher risk for CHF than no CKD (Table 2).

Acute Therapy and In-hospital Procedures

Among patients presenting with STEMI, the odds ratio for any reperfusion therapy was significantly lower with worsening CKD stage (p-value $_{(trend)}$=0.0005, Table 2) after adjustment for baseline features. However, the use of primary PCI (p-value $_{(trend)}$=0.75, Table 2) and thrombolytics (p-value $_{(trend)}$=0.65) was similar after accounting for baseline differences. Among those presenting with NSTEMI, patients with CKD were less likely to undergo early invasive therapy (p-value $_{(trend)}$<0.0001) or any revascularization (p-value $_{(trend)}$<0.0001; Table 2).

Patients presenting with either STEMI or NSTEMI also had higher rates of major bleeding (Table 3) with advancing CKD stage; notably, rates were similar among those with Stage 4 and Stage 5 CKD. CKD patients presenting with either STEMI or NSTEMI had excess dosing of Glycoprotein IIb/IIIa inhibitors (GPI, p-value<0.0001 for trend). For patients presenting with STEMI, those without CKD had a 2.2% rate of Glycoprotein IIb/IIIa inhibitors (GPI) overdosing, compared with 55.6% among those with Stage 5 CKD (p-value $_{(trend)}$<0.0001; Table 3). For patients with NSTEMI, the rate of GPI overdosing ranged from 2.2% among patients without CKD to 40.9% among patients with Stage 5 CKD (p-value $_{(trend)}$<0.0001; Table 3).

Acute In-hospital and Discharge Cardio-Protective Medications and Counseling

Rates of acute (within 24-hours) in-hospital aspirin use were substantially lower among those with more advanced CKD (p-value $_{(trend)}$<0.001 for STEMI and NSTEMI, Figure 3). Similarly, use of clopidogrel, beta blockers, and statins were generally lower among patients with more advanced CKD (all p-value $_{(trend)}$<0.0001). In general, similar observations were made for discharge medications. Rates of smoking cessation, dietary and exercise counseling and referral to cardiac rehabilitation were generally lower for patients with more advanced CKD stage (Figure 3).

Comment

Principal Findings

Overall, nearly one-third of patients presenting with STEMI and more than 40% of patients presenting with NSTEMI in this real-world registry had CKD, substantially higher than previously recognized in the ACS population. Adjusted rates of adverse outcomes were markedly higher among patients with progressively worse CKD, with odds ratios for death being 4 to 8 times higher among those with Stage 5 CKD than patients without CKD. The current study also documented lower utilization of acute therapies, in-hospital procedures, cardioprotective medications, and higher rates of medication overdosing among patients with CKD. Finally, despite these high rates of adverse outcomes, patients with CKD were less likely to receive discharge counseling related to cardiovascular disease risk reduction.

In the Context of the Current Literature

Patients with CKD, and particularly those undergoing dialysis, are known to have poor outcomes following MI.[10–15;21–24] Using the United States Renal Data System database from 1977–1995, patients on chronic dialysis therapy had an overall mortality rate of nearly 90% at 5-years; among patients with myocardial infarction, almost half experience a cardiac-related death within two-years.[10] Even using more contemporary data (1998–2000), patients on dialysis presenting with a myocardial infarction were far more likely to die as compared to patients with MI not on dialysis.[14] In addition, the use of coronary interventions and cardio-protective medications among patients with CKD or on dialysis has been shown to be sub-optimal.[13;27–30]

Previous work from the GRACE Registry demonstrated that nearly one-third of patients presenting with STEMI or NSTEMI had CKD.[18] Renal sub-group analyses of clinical trials have demonstrated CKD prevalence of 15 to 25% and associated with an increased risk of death,[16;17] albeit not as strong as observed in the present study. Data from the CRUSADE registry initially suggested that nearly 15% of the NSTEMI population had renal dysfunction as defined dichotomously as serum creatinine >2.0 mg/dl (actual serum creatinine values were not available)[19]; our findings suggest that nearly 40% of those presenting with NSTEMI have CKD. More contemporary data using the MDRD equation is more consistent with the findings in the present paper.[20]

Our data allowed for comparison of the relationship between CKD and outcomes among patients with both types of MI (NSTEMI and STEMI) collected simultaneously at a single set of hospitals. Though outcomes were poor in patients with CKD with both types of MI, one of the more novel findings in the present study was the observation that progressive CKD stage was associated with a steeper gradient of mortality among those presenting with STEMI and CKD as compared to NSTEMI and CKD.

The findings from the present study extend the current literature in several important ways. First, these data are derived using a large, nationally representative, real-world registry that

included patients from a large number of medical institutions. In addition, several prior studies of outcomes associated with CKD for patients with STEMI and NSTEMI were generated from clinical trials, which tend to exclude patients with advanced renal disease and to encourage specific care patterns. As such, clinical trial data likely underestimates the true burden and severity of CKD in the MI population, as well as preventing an accurate assessment of procedure and medication utilization. Secondly, the current data include not only dialysis patients, but also individuals with Stage 3 and 4 CKD, the groups that comprise the largest burden of CKD in the United States.[31] This allowed for a more comprehensive assessment of CKD in the post-MI population. Third, the current study used data derived from 2007, allowing for an understanding of the contemporary experience of patients with CKD. This is particularly important in the context that in 2002, several key articles described the increased mortality of patients with CKD in the AMI setting, and the relative under-utilization as compared to patients without CKD.[21–24] Thus, several years later, limited progress has been made.

Potential Mechanisms for Worse Clinical Outcomes

Patients with CKD have higher rates of pre-existing CVD, and more severe CVD upon presentation with ACS, which in part may contribute to their poorer outcomes. In addition, the findings from the present study, and work from prior studies, indicates under-utilization of known cardio-protective therapies in patients with CKD and more frequent errors in dosing when used, which may further contribute to the poor outcomes observed in this group. Indeed, many therapies have not specifically been studied in CKD and in patients on dialysis as nephrology patients are the least likely of all internal medicine sub-specialty patients to be studied in clinical trials.[25;26]

Further, there are data to suggest that known interventions and proven therapies in the general population may not provide benefits to end-stage renal disease patients. For example, the 4-D trial, which enrolled patients with diabetes and end-stage renal disease on dialysis, demonstrated increased risk of fatal stroke among those randomized to statin therapy versus placebo.[32] Therefore, the avoidance of certain cardio-protective medications in dialysis patients may in part be driven by the lack of clinical trial data to support their efficacy, rather than by errors of omission. The reduced utilization of invasive procedures particularly in NSTEMI patients where decision making is less protocol or critical pathway driven than STEMI, may also reflect a desire to balance cardio-protective effects of procedures with the desire to avoid further damaging kidney function. This may be reflected by the lowest relative utilization of cardiac catheterization, PCI or CABG in stage 4 CKD rather than stage 5 CKD (ESRD), a finding that was more pronounced among NSTEMI patients.

The rate of complications in patients with CKD, particularly excess bleeding in part related to the use of antithrombin and anti-platelet medications, may limit the efficacy of known interventions.[33;34] Data from the present study confirm the high rate of major bleeding among Stage 5 CKD, and extends these findings to Stages 3 and 4 CKD, which demonstrate a similarly increased risk of these complications as well. This increase in bleeding may be related to intrinsic platelet dysfunction related to CKD as well as excessive dosing of medications in patients with CKD.[35;36]

While the use of invasive procedures may be limited in part by a desire to avoid worsening kidney function, and the use of medications may be limited by an absent evidence basis or concerns for complications, no clear barriers should exist for low-risk interventions such as discharge counseling. We observed a lower rate of counseling for life-style modification by CKD stage, among those considered to have no contraindication for an intervention.

Strengths and Limitations

The major strength of the current study includes the use of a nationally-representative registry, providing real-world data that are more generalizable than results from single center registries. These data extend previous data using binary cutpoints or focusing on dialysis patients by demonstrating gradients of risk and therapy utilization by severity of CKD. Additionally, the use of registry data eliminates the selection bias of clinical trials. Further, we had very large numbers of patients with CKD presenting with both STEMI and NSTEMI, enabling a detailed analysis by CKD stage and MI type. We were also able to examine post-MI outcomes and processes at several levels, including in-hospital clinical outcomes, procedure utilization, and cardio-protective medication and counseling use. Certain limitations of the current analysis warrant discussion. As the data are derived from a hospital-based registry, patients who died prior to admission to the hospital were by definition excluded from the registry and therefore mortality may be underestimated. Further, we evaluated only short-term inhospital outcomes; however, long-term outcomes related to CKD and dialysis post-MI have been previously described.[10;14] Data were extracted from hospitals with differing creatinine assays and standards, and no standard central determination of kidney function was performed. However these data reflect actual clinical practice, and the information about kidney function that was available to treating physicians when therapeutic decisions were made. There were too few patients with eGFR<15 to separately examine those not on dialysis. Lastly, we did not have information on albuminuria and proteinuria.

Implications

The most striking finding from this study is the high rate of CKD in the MI population. Clinicians should be aware of the high likelihood of concomitant CKD and CVD in patients presenting with MI to allow for appropriate treatment decisions and to adjust medication dosing. In addition, these findings underscore the high mortality rates and frequent adverse outcomes associated with CKD in the setting of MI, and the need to direct clinical trials aimed specifically at this high-risk sub-group in order to identify optimal therapies and treatment for these patients. The underutilization of evidence based therapies, procedures and counseling in the CKD population is an opportunity for quality improvement in the care of high-risk patients.

Conclusions

Reports over the past decade have highlighted the importance of CKD among patients with MI. Data from this contemporary cohort suggest patients with CKD still receive fewer evidence-based therapies and have substantially higher mortality rates. Additional research to define optimal post-MI care in patients with CKD is warranted.

Short Commentary

Chronic kidney disease (CKD) is a risk factor for myocardial infarction (MI) and death. We sought to characterize the association between CKD severity and short-term outcomes and the use of in-hospital evidence-based therapies among patients with STEMI and NSTEMI using the ACTION registry, a nation-wide sample of STEMI and NSTEMI patients admitted to hospitals in the United States. Overall, 30.5% and 42.9% of patients with STEMI and NSTEMI, respectively, had CKD. Regardless of MI type, patients with progressively more severe CKD had higher rates of death. In addition, patients with progressively more severe CKD were less likely to receive acute evidence-based therapies including aspirin, beta-blockers or clopidogrel, undergo any reperfusion (STEMI) or revascularization (NSTEMI), and had higher rates of bleeding. We conclude that a large proportion of patients presenting with STEMI or NSTEMI have CKD and have increased in-hospital mortality rates. These

patients receive fewer evidence-based therapies. Additional research to define optimal post-MI care in patients with CKD is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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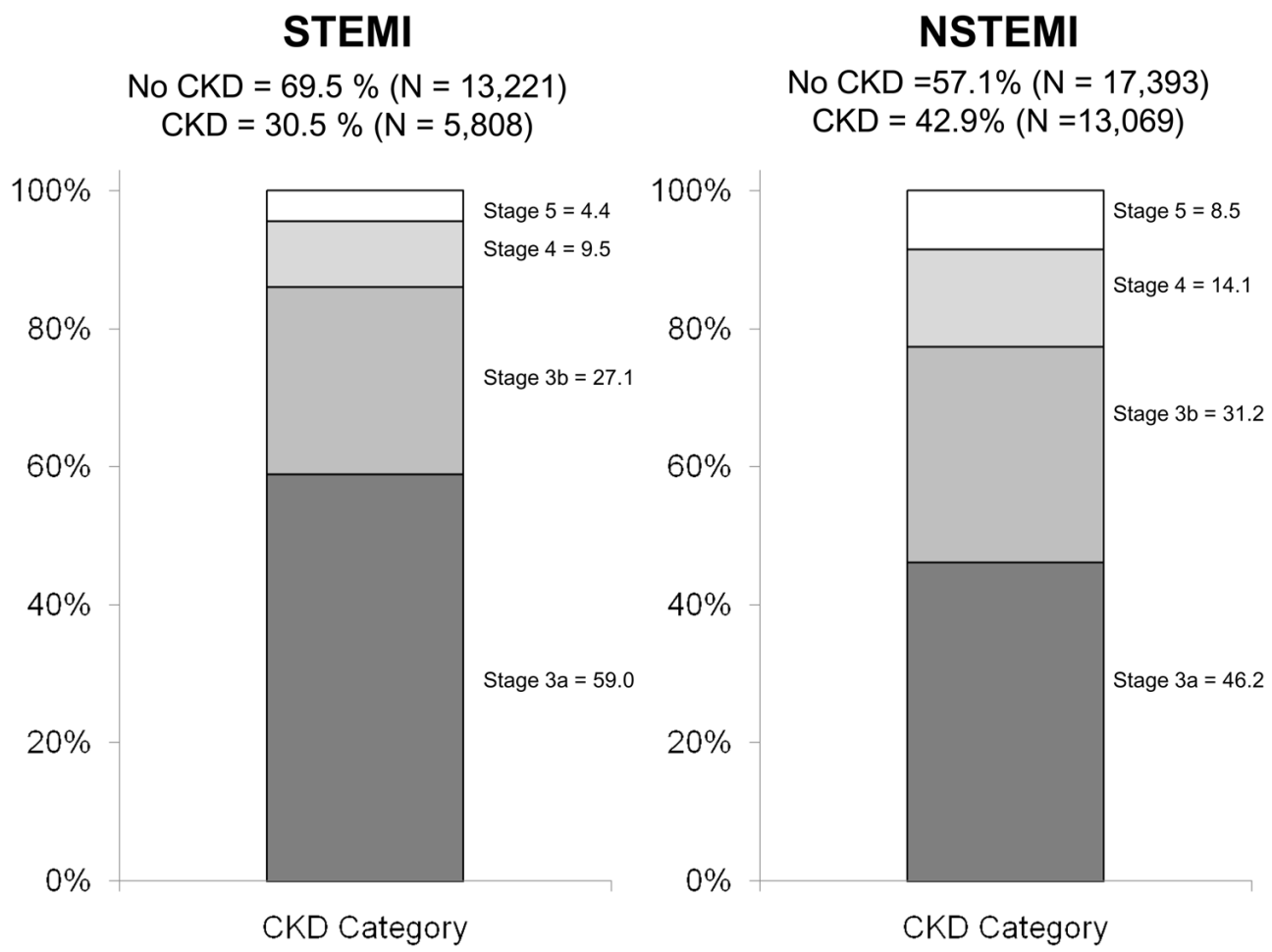

Figure 1.
Prevalence of CKD and Stages 3a, 3b, 4, and 5 (no dialysis), and dialysis presenting with STEMI and NSTEMI. The “no CKD” category is limited by lack of information on albuminuria.

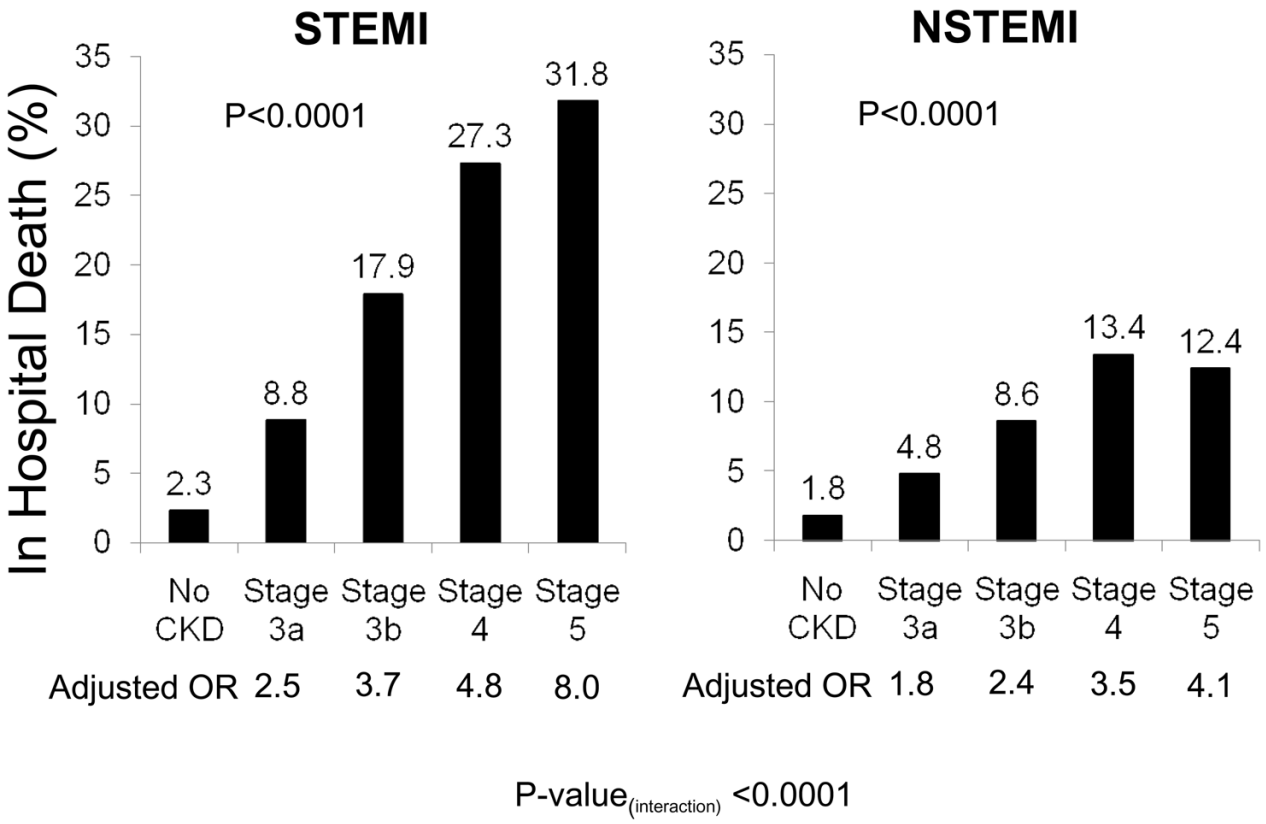

Figure 2.
Crude rates and adjusted odds ratios for death by CKD stages among those presenting with STEMI and NSTEMI; p-values(trend); p-value(interaction) test for STEMI vs. NSTEMI by CKD stages. The “no CKD” category is limited by lack of information on albuminuria.

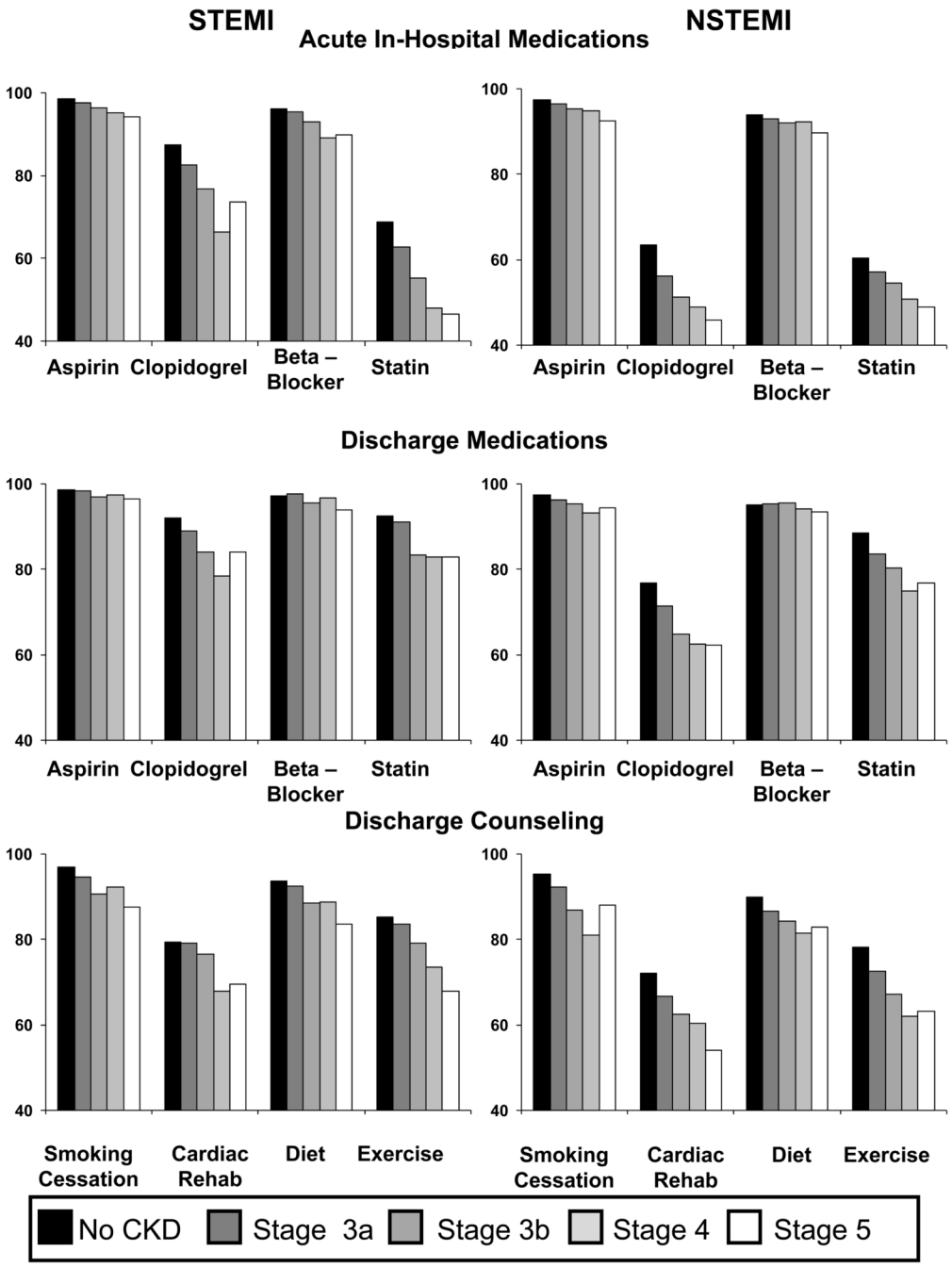

Figure 3.

Crude rates of acute in-hospital medications (within 24-hours), discharge medications, and discharge counseling by CKD status. All p-values test for trend across CKD stage <0.001 except for Aspirin as a discharge medication and referral to cardiac rehabilitation (STEMI; p-values(trend)=0.02 for both), and beta blockers as a discharge medication (p-values(trend) =0.50 [STEMI], p-values(trend)=0.12 [NSTEMI]). The “no CKD” category is limited by lack of information on albuminuria.

Table 1

Presenting characteristics by CKD Stage

STEMI							
	No CKD[¥]	**Stage 3a CKD**	**Stage 3b CKD**	**Stage 4 CKD**	**Stage 5 CKD (no dialysis)**	**Dialysis**	**p-value[+]**
Sample Size	13221	3427	1574	554	87	166	
Age, years[*]	57 (49, 66)	68 (59, 77)	75 (64, 83)	77 (66,85)	74 (63, 82)	65 (57, 75)	<0.0001
Women, %	24.1	39.7	50.5	57.9	57.5	51.2	<0.0001
Race							
White, %	84.2	89.0	87.0	85.7	81.6	60.2	0.0032
Black, %	8.0	4.6	5.3	6.3	10.3	28.9	
Hispanic, %	3.7	2.7	3.1	3.8	3.4	4.8	
Other, %	2.9	2.3	2.5	2.5	3.4	3.0	
Estimated Glomerular Filtration Rate, ml/min/1.73m^2[*]	79.6 (69.7, 92.5)	53.8 (50.0, 57.1)	38.9 (35.1, 42.3)	24.9 (21.2, 27.6)	12.3 (9.4, 13.7)	NA	<0.0001
Body Mass Index, kg/m^2[*]	28.3 (25.1, 32.1)	27.8 (24.7, 31.7)	27.4 (24.2, 31.4)	27.2 (23.6, 31.7)	25.7 (22.8, 30.4)	27.5 (23.4, 31.0)	<0.0001
Hypertension, %	54.6	68.0	80.2	83.4	79.3	88.0	<0.0001
Diabetes, %	19.3	23.9	34.2	40.3	47.1	63.9	<0.0001
Current Smoking, %	48.8	30.8	22.0	19.5	16.1	22.9	<0.0001
Peak Troponin[**]	91.2	91.0	90.9	89.5	93.2	88.7	0.22
Peak CK-MB[**]	73.1	71.2	67.3	62.6	52.2	50.7	0.0002
Prior Myocardial Infarction, %	17.5	19.5	23.8	24.9	28.7	30.7	<0.0001
Prior CHF, %	2.8	6.4	15.2	19.3	19.5	34.3	<0.0001
Prior Stroke, %	3.5	6.5	12.4	15.7	14.9	18.1	<0.0001
NSTEMI							
Sample Size	17,393	6,031	4,081	1,846	312	799	
Age, years[*]	60 (52,71)	73 (64, 81)	79 (70, 85)	80 (70,86)	75 (62.5, 83)	68 (59, 77)	<0.0001
Women, %	31.1	47.1	53.0	57.5	50.6	44.6	<0.0001
Race							
White, %	83.4	88.4	87.2	86.0	70.2	60.8	0.20
Black, %	9.6	6.1	6.9	7.4	17.9	25.9	

STEMI							
	No CKD[¥]	**Stage 3a CKD**	**Stage 3b CKD**	**Stage 4 CKD**	**Stage 5 CKD (no dialysis)**	**Dialysis**	**p-value[+]**
Hispanic, %	3.7	2.6	2.8	2.9	5.4	7.5	
Other, %	2.1	1.6	1.8	1.7	3.5	2.9	
Estimated Glomerular Filtration Rate, ml/min/1.73m^2[*]	79.1 (69.5, 92.3)	52.7 (49.4, 56.5)	38.3 (34.7, 41.7)	24.6 (20.7, 27.5)	12.1 (9.6, 13.7)	NA	<0.0001
Body Mass Index, kg/m^2[*]	28.6 (25.1, 32.9)	28.0 (24.6, 32.1)	27.5 (23.9, 32.1)	27.3 (23.7, 32.0)	27.5 (23.3, 33.1)	26.7 (23.5, 31.4)	<0.0001
Hypertension, %	65.0	79.2	85.1	86.4	89.7	89.9	<0.0001
Diabetes, %	25.8	36.0	48.3	53.7	55.1	68.6	<0.0001
Current Smoking, %	38.1	19.3	14.4	12.4	17.6	16.6	<0.0001
Peak Troponin[**]	78.8	79.2	79.2	80.4	78.6	79.2	<0.0001
Peak CK-MB[**]	43.1	38.4	33.9	34.8	35.1	27.0	<0.0001
Prior Myocardial Infarction, %	22.9	29.6	34.4	36.7	30.8	40.3	<0.0001
Prior CHF, %	7.6	17.2	31.0	39.1	38.8	42.6	<0.0001
Prior Stroke, %	6.1	11.4	15.2	16.2	13.8	20.2	<0.0001

[*] Presented as median (25th, 75th percentiles).

[+] P-values test for trend

[**] presented as the % with >5 times the upper limit of normal; peak troponin levels vary by assay type and reference ranges across different hospital sites

[¥] The “no CKD” category is limited by the lack of albuminuria

Table 2

Crude rates and adjusted odds ratios for in-hospital outcomes and in-hospital procedures by CKD Stage**; n represents the number of events

	No CKD¥	Stage 3a CKD	Stage 3b CKD	Stage 4 CKD	Stage 5 CKD or dialysis	p-value+
STEMI						
CHF, % (n)	4.2 (516)	9.1 (286)	13.6 (195)	19.1 (98)	14.6 (34)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	1.7 (1.4–2.1)	2.3 (1.9–2.7)	3.1 (2.4–4.1)	2.8 (2.0–3.9)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (ref)	1.5 (1.2–1.8)	1.6 (1.3–1.9)	1.8 (1.3–2.4)	1.5 (1.1–2.1)	<0.0001
Primary PCI (STEMI), % (n)	87.1 (9586)	84.6 (2283)	81.4 (857)	75.4 (230)	71.3 (102)	0.84
Age, race, sex adjusted OR (95% CI)	1.0 (Ref)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.8 (0.6–1.1)	1.0 (0.6–1.8)	0.81
Multivariable adjusted OR (95% CI)*	1.0 (Ref)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.8 (0.6–1.2)	1.0 (0.6–1.8)	0.75
Any Reperfusion§, % (n)	95.2 (10484)	92.5 (2495)	88.9 (936)	83.6 (255)	78.3 (112)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (Ref)	0.8 (0.7–1.0)	0.7 (0.6–0.8)	0.5 (0.4–0.6)	0.4 (0.3–0.5)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (Ref)	0.9 (0.8–1.1)	0.9 (0.7–1.1)	0.6 (0.5–0.8)	0.6 (0.4–0.9)	0.0005
NSTEMI						
CHF, % (n)	4.4 (691)	8.3 (454)	12.6 (470)	17.3 (296)	11.6 (118)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	1.6 (1.4–1.8)	2.1 (1.8–2.5)	2.9 (2.4–3.5)	2.2 (1.8–2.8)	<0.0001
Multivariable adjusted OR (95% CI)	1.0 (ref)	1.3 (1.2–1.5)	1.5 (1.3–1.7)	1.9 (1.6–2.3)	1.3 (1.1–1.6)	<0.0001
Early Invasive (NSTEMI), % (n)	77.8 (12516)	67.7 (3433)	54.7 (1614)	36.7 (383)	48.9 (372)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	0.8 (0.7–0.9)	0.5 (0.5–0.6)	0.3 (0.2–0.3)	0.4 (0.3–0.5)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (ref)	0.9 (0.8–1.0)	0.7 (0.6–0.8)	0.4 (0.3–0.5)	0.6 (0.5–0.7)	<0.0001
Any Revascularization€, % (n)	71.8 (10491)	62.0 (2868)	50.8 (1356)	41.2 (387)	48.9 (334)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (Ref)	0.8 (0.8–0.9)	0.6 (0.5–0.6)	0.5 (0.4–0.5)	0.5 (0.4–0.7)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (Ref)	0.9 (0.9–1.0)	0.7 (0.7–0.8)	0.6 (0.5–0.7)	0.8 (0.7–1.0)	<0.0001

*Multivariable models adjusted for age, gender, body mass index (BMI), race, insurance status, hypertension, diabetes, recent/current smoker, hypercholesterolemia, prior PAD, prior MI, prior percutaneous coronary intervention, prior coronary bypass graft surgery, history of heart failure, history of stroke, signs of heart failure, admission heart rate and systolic blood pressure.

+P-values test for trend

**Denominators may vary based on the individual exclusions for different outcomes

¥The “no CKD” category is limited by the lack of albuminuria

[§] Any reperfusion defined as use of primary PCI or fibrinolytic medications

[€] Any revascularization defined as PCI or CABG

OR, odds ratio; CI, confidence interval.

Table 3

Crude rates and adjusted odds ratios in-hospital adverse outcomes by CKD Stage**; n represents the number of events

	No CKD¥	Stage 3a CKD	Stage 3b CKD	Stage 4 CKD	Stage 5 CKD or dialysis	p-value+
STEMI						
Non-CABG Major Bleed, % (n)	8.8 (999)	14.7 (420)	23.1 (304)	26.6 (128)	26.4 (58)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	1.5 (1.3–1.7)	2.4 (2.0–2.8)	2.7 (2.2–3.3)	2.8 (2.0–3.9)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (ref)	1.4 (1.2–1.6)	2.0 (1.7–2.4)	2.0 (1.6–2.5)	2.1 (1.4–2.9)	<0.0001
GP IIb/IIIa Excess Dosing	2.2 (114)	19.1 (250)	49.2 (216)	57.0 (57)	55.6 (10)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	5.1 (4.0–6.5)	21.3 (14.5–31.3)	25.9 (12.1–55.7)	39.1 (14.1–108.2)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (ref)	6.4 (4.9–8.2)	38.0 (22.0–65.9)	42.7 (16.3–112.2)	51.0 (16.0–162.6)	<0.0001
Anti-thrombin Excess dosing€	72.3 (832)	74.9 (206)	72.2 (70)	80.8 (21)	37.5 (3)	0.45
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	1.2 (0.9–1.6)	1.2 (0.7–1.8)	1.8 (0.6–5.4)	0.3 (0.1–0.7)	0.53
Multivariable adjusted OR (95% CI)*	1.0 (ref)	1.2 (0.9–1.7)	1.2 (0.7–1.8)	1.9 (0.6–6.3)	0.3 (0.1–0.7)	0.44
NSTEMI						
Non-CABG Major Bleed, % (n)	5.8 (789)	11.2 (546)	14.9 (507)	22.7 (366)	20.2 (187)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	1.9 (1.6–2.2)	2.5 (2.1–2.9)	4.0 (3.4–4.8)	3.4 (2.8–4.2)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (ref)	1.7 (1.5–1.9)	2.0 (1.7–2.3)	3.2 (2.7–3.8)	2.4 (1.9–2.9)	<0.0001
GP IIb/IIIa Excess Dosing	2.2 (183)	20.7 (433)	44.4 (447)	44.4 (127)	40.9 (47)	<0.0001
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	5.6 (4.6–6.8)	13.3 (10.3–17.3)	14.3 (9.4–21.9)	18.8 (10.7–33.2)	<0.0001
Multivariable adjusted OR (95% CI)*	1.0 (ref)	6.3 (5.2–7.7)	18.5 (13.5–25.4)	20.2 (12.1–33.9)	22.7 (11.8–44.0)	<0.0001
Anti-thrombin Excess Dosing€	22.2 (3273)	23.4 (1138)	24.5 (767)	23.8 (308)	28.4 (213)	0.0003
Age, race, sex adjusted OR (95% CI)	1.0 (ref)	1.0 (0.9–1.0)	1.0 (0.9–1.1)	1.0 (0.8–1.1)	1.2 (1.1–1.4)	0.37
Multivariable adjusted OR (95% CI)*	1.0 (ref)	1.0 (1.0–1.1)	1.1 (1.0–1.2)	1.0 (0.9–1.2)	1.2 (1.0–1.4)	0.07

*Multivariable models adjusted for age, gender, body mass index (BMI), race, insurance status, hypertension, diabetes, recent/current smoker, hypercholesterolemia, prior PAD, prior MI, prior percutaneous coronary intervention, prior coronary bypass graft surgery, history of heart failure, history of stroke, signs of heart failure, admission heart rate and systolic blood pressure.

+P-values test for trend

**Denominators may vary based on the individual exclusions for different outcomes

¥The "no CKD" category is limited by the lack of albuminuria OR, odds ratio; CI, confidence interval.

€Includes dosing above guideline recommendations for unfractionated heparin (UFH) with fibrinolytics in STEMI, and for UFH or low molecular weight heparin for NSTEMI.